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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1612	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,778	YOSHINO ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4 pages / 08/08/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on April 29, 2009.

Election/Restrictions

Applicant's election of the following species: 3-methyl-1-phenyl-2-pyrazoline-5-on (edaravone) as the compound of formula I in the reply filed on April 29, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a).

Status of Claims

Claims 1-32 are currently pending and are the subject of this office action.

Claims 1-32 are presently under examination.

Priority

The present application is a 371 of PCT/JP05/001932 filed on 02/09/05, and claims priority to foreign application: JAPAN 2004-032420 filed on 02/09/2004 and JAPAN 2004-032421 filed on 02/09/2004.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action. 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

Information Disclosure Statement

The Information Disclosure Statement filed on August 8, 2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 8 and 9 recite pyrazolone derivative or solvate.

M.P.E.P. #2163 states: “An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the

claimed invention….one must define a compound by 'whatever characteristics sufficiently distinguish it'. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process".

The terms derivative and solvate, correspond in some undefined way to specifically instantly disclosed chemicals. None of these meet the written description provision of USC 112, first paragraph, due to lack of chemical structural information for what they are since chemical structures are highly variant and encompass a myriad of possibilities. The skilled artisan cannot envision the detailed chemical structures encompassed by derivatives and solvates.

Given the broad scope of the subject claimed matter, Applicant has not provided sufficient written description that would allow the skilled artisan to recognize all the pyrazolone derivatives and solvates claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 17-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17-32 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: there is no body claim: the claim does not set forth any steps involved in the method/process, it is unclear what method/process Applicant is intended to encompass.

Prior Art: counterpart

WO 02/34264 is the PCT counterpart to US 6,933,310.

WO 02/34264 has a 102(b) date as a result of its May 2, 2002 publication date.

US 6,943,185 is prior art under U.S.C 102(e) as a result of its August 23, 2005 publication date.

Because WO 02/34264 and US 6,933,310 appear to have identical disclosures, and because the WO document was published in Japanese language designating the United States, the US Patent US US 6,933,310, which is the National Stage entry of WO 02/34264 is being used as a translation of WO 02/34264 PCT. As such, any reference hereinafter to column and line numbers will be based upon the US Patent, but should be interpreted as referring to the corresponding disclosure of the aforementioned PCT counterpart.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ikeda (WO 02/34264, cited by Applicant, which is the PCT counterpart to US 6,933,310, see above prior art counterpart).

Claims 1-7 recite a method of treating amyotrophic lateral sclerosis (AML) or symptoms caused by amyotrophic lateral sclerosis and/or suppressing the progression thereof, which comprises administering to a patient in need thereof as an active ingredient: edaravone (species elected), under the condition that a drug holiday period of 1 day or more is provided once, twice or more during the period for treating the disease or suppressing the progression of the disease.

Claim 3 further limits claim 1, wherein the drug holiday period is provided after a drug administration period of about 7 to 14 days.

Claim 4 further limits claim 1, wherein a second subsequent drug administration period is about 5 to 14 days.

Claim 5 further limits claim 1, wherein the drug holiday period is about 14 to 16 days.

Claim 6 further limits claim 1, wherein the drug administration period and the drug administration period are each 14 days.

Claim 7 further limits claim 1, wherein a course consisting of an initial drug administration period of 14 days and a drug holiday period of 14 days is provided, followed by repetitions of the following combination of periods: drug administration period: 5 days per week for 2 weeks; and drug holiday period: 14 days.

For claims 1-7, Ikeda teaches a method of treating amyotrophic lateral sclerosis comprising the administration of 3-methyl-1-phenyl-2-pirazoline-5-on (edaravone) (see for example claims 1-5). Ikeda further teaches that the route of administration of the medicament is not particularly limited (see column 5, lines 10-14) and that the medicament can be administered directly to the patient preferably in the form of a pharmaceutical composition (see column 5, lines 15-21). The dose of the medicament can be selected according to various conditions including type of disease being treated, progress of the disease or degree of the symptoms, and age and weight of the patient (see column 5, lines 53-57).

Ikeda does not teach the specific dose regimens which includes holiday periods as disclosed in claims 1-7. However, it's within the capability of the ordinary artisan to determine a specific dose regimen for a particular patient (see underline statement by Ikeda above) and adjust dose regimens based on the observed clinical effectiveness, thus resulting in the practice of claims 1-7 with a reasonable expectation of success.

Claim 8 further limits claim 1, wherein the daily dose contains about 15 to 240 mg of edaravone.

Claim 9 further limits claim 1, wherein the daily dose contains about 60 mg of edaravone.

For claims 8 and 9, Ikeda further teaches a daily dosage of approximately 0.01 microgram/kg to 10 mg/kg for an adult by injection or drip, which translates into 0.0008 mg/day (0.01 microgram/kg/day x 80 kg for an adult) to 800 mg/day (10 mg/kg/day x 80 kg), which clearly overlap the dosage of claims 8 and 9. MPEP 2144.05 states: In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990).

Claim 10 further limits claim 1, wherein the administration is carried out once daily.

Claim 11, further limits claim 1, wherein the administration is a continuous administration.

Claim 12, further limits claim 11, wherein the continuous administration is intravenous infusion administration.

Claim 13 further limits claim 12, wherein the administration rate in the intravenous infusion administration is about 0.5 to 1 mg/minute.

Claim 14 further limits claim11, wherein the continuous administration is an administration form that is substantially equivalent to the intravenous infusion administration wherein the amount of ederavone is administered at 0.5 to 1 mg per minute.

For claims 10-14, Ikeda further teaches that: the dose of the medicament can be selected according to various conditions including type of disease being treated, progress of the disease or degree of the symptoms, and age and weight of the patient. In general approximately 0.01 microgram/kg to 10 mg/kg per day for an adult is administered by injection or drip (see column 5, lines 52-63). Ikeda also teaches that the route of administration is not particularly limited, and it can be administered orally or parenterally (for example, intravenous, intramuscular, hypodermic or intradermal injections, or inhalation) (see column 5, lines 10-14).

Ikeda does not teach a once daily or a continuous administration, however it's within the capability of the ordinary artisan to determine a specific mode of administration for a particular patient and adjust dosage amounts based on the observed clinical effectiveness, thus resulting in the practice of claims 10-14 with a reasonable expectation of success.

Claims 15 and 16 further limit claim 1, wherein certain symptoms caused by ALS like: decreased respiratory function, voice and speech disorders, dysphagia, or upper and lower extremity motor disorders are being treated.

For claims 15 and 16, Ikeda teaches that ALS often begins at middle age, and is a lethal intractable disease, in which the condition rapidly deteriorates from muscular atrophy and muscle weakness to, finally, death due to respiratory insufficiency or the like in a matter of a few years (see column 1, lines 28-34). Ikeda further teaches that ALS is a cryptogenic disease mainly characterized by muscular atrophy and

fasciculation. The initial symptoms mainly include hand weakness, dyskinesia in the digits and hands, and fasciculation in the upper limbs, And ALS can be classified into upper limb type, bulbar type, lower limb type and mixed type according to onset site. With any type of the disease, muscle groups of the whole body are impinged with the progress of the symptoms (see column 4, lines 27-38).

Conclusion

No claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1612
August 14, 2009

/Brandon J Fetterolf/

Primary Examiner, Art Unit 1642